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GLAXOSMITHKLINE

CORPORATE INTELLECTUAL PROPERTY, MAI B475

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RESEARCH TRIANGLE PARK, NC 27709-3398

EXAMINER

GANGLE, BRIAN J

ART UNIT

PAPER NUMBER

1645

NOTIFICATION DATE

DELIVERY MODE

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ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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ADVISORY ACTION

The amendment filed on 4/7/2008 under 37 DFR 1.116, in reply to the final rejection, has been considered but is not deemed to place the application in condition for allowance. The amendment is entered.

Claims 1, 6-7, and 11-14 are pending. Claims 1 and 6 are amended. Claims 1 and 6-7 are currently under examination.

Applicant's request for reconsideration of the finality of the rejection of the last Office action is not persuasive for the following reasons.

Applicant argues:

1. That the office action of 2/6/2008 should not have been made final because the examiner made new rejections that were not necessitated by applicant's amendments to the claims. Applicant asserts that the amendment to independent claim 1 incorporated the subject matter previously presented in claim 5 (strain CU-385) and provided for a specific strain (B:4:P1.7b,4) exemplified in example 8 of the instant specification. Applicant argues that the amended claim encompassed subject matter encompassed by the previously presented claim and which should reasonably have been expected to be claimed, as it was disclosed in the examples of the specification.

Applicant's arguments have been fully considered and deemed non-persuasive.

Until applicant's amendment, filed on 11/9/2007, there was no claim that required strain CU-385 and B:4:P1.7b,4. In fact, no claim at all mentioned strain B:4:P1.7b,4, and claim 5, which did require CU-385, encompassed the very large genus of blebs that were "not deficient in PorA compared to blebs made from strain H44/76." As acknowledged by applicant in the interview of 10/24/2007, the unamended claims were anticipated by the cited prior art. The provision in MPEP 904.02 that a search should cover the claimed subject matter and should also cover the disclosed features which might reasonably be expected to be claimed does not preclude an examiner from making the second or any subsequent office action on the merits final if the office action contains a new ground of rejection that was necessitated solely by applicant's amendment of the claims to eliminate an unpatentable alternative. An examiner cannot be

expected to foresee whether or how an applicant will amend a claim to overcome a rejection except in very limited circumstances (e.g., whether the examiner suggests how applicant can overcome a rejection under 35 USC 112, second paragraph). Therefore, applicant's decision to reduce the scope of the claims in order to eliminate unpatentable subject matter necessitated the new grounds of rejection, and the office action of 2/6/2008 was properly made final.

Claim Objections Withdrawn

The objection to claims 1, 6, and 7 because claim 1 recites the serosubtype "B:4:P1.7,b,4," is withdrawn in light of applicant's amendment thereto.

Claim Rejections Withdrawn

The rejection of claims 6-7 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for multivalent vaccines providing protection against *Neisseria meningitidis*, does not reasonably provide enablement for multivalent vaccines for protection against neisserial disease, is withdrawn in light of applicant's amendment thereto.

The rejection of claim 1, under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "a first bleb preparation deficient in PorA derived from the *Neisseria meningitidis* B CU-385 strain," is withdrawn in light of applicant's amendment thereto.

The rejection of claim 1, under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "a second bleb preparation that is not deficient in PorA derived from a *Neisseria meningitidis* B:4:P1.7b,4 strain prevalent in New Zealand," is withdrawn in light of applicant's amendment thereto.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 1, 6, and 7, under 35 U.S.C. 103(a) as being unpatentable over Berthet *et al.* (PCT Publication WO 01/09350, 2/8/2001) in view of Vermont *et al.* (Infect. Immun., 70:584-590, 2/2002) and Baker *et al.* (J. Paediatr. Child Health, 37:S13-S19, 2001), is maintained for the reasons set forth in the previous office action.

Applicant argues:

1. That one of ordinary skill in the art would not have been motivated to prepare a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA and a second bleb preparation that is not deficient in PorA.

2. That Berthet sought to provide methods to optimize bleb vaccines by deleting immunodominant variable outer membrane proteins such as PorA, while Vermont examined PorA-based meningococcal OMV vaccines responses against serosubtype P1.7-2,4. Applicant asserts that one would not have been motivated to combine a vaccine which sought to delete PorA with one that was PorA specific as each was seeking an opposite response.

3. That Baker does not remedy the deficiencies of Berthet and Vermont as Baker only discusses the potential value of a P1.7b,4 PorA specific vaccine in controlling New Zealand's meningococcal epidemic. Applicant asserts that Baker does not disclose or suggest how to make such a vaccine.

4. That the results of the combination of references would not be predictable. Applicant has submitted a letter in response to the PCT Written Opinion that applicant asserts includes data showing the technical contribution to the art of the bleb preparations of the present invention.

5. That that cited art does not include each element as claimed. Applicant asserts that Berthet does not disclose a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA, wherein the first bleb preparation is derived from CU-385. Applicant also asserts that the bleb preparations of Berthet's invention are from a single modified strain in which one or more of their processes are used.

6. That Berthet teaches away from using a CU-385 strain as a meningococcal B bleb preparation strain. Applicant asserts that Berthet suggests that their production strain has a

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different PorA type than the heterologous strains against which immunoprotection is measured (including CU-385).

7. That page 36, as cited by the examiner, “does not discuss multivalent bleb preparations of the invention, but instead provides for the use of wild-type meningococcus B bleb preparations from 2 or more strains or a meningococcus B bleb preparations of the invention as an envisaged combination with meningococcal polysaccharides.”

8. That applicant’s multivalent composition does not require additional meningococcal polysaccharides to provide satisfactory serum bactericidal activity.

9. That Vermont and Baker do not make up for the deficiencies of Berthet. Applicant asserts that Vermont only evaluates the avidity maturation and IgG isotype distribution of antibodies after vaccination with a monovalent meningococcal B OMV (serosubtype P1.7-2,4) and Baker only discusses the potential value of a P1.7b,4 PorA specific vaccine in controlling New Zealand’s meningococcal epidemic, but do not disclose how to make such a vaccine.

Applicant’s arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the claims are not drawn to a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA and a second bleb preparation that is not deficient in PorA. All that is required to meet the claim limitations is a bleb composition comprising blebs from CU-385 and blebs from strain B:4:P1.7b,4. The reasons behind combining these do not need to be the same as applicant’s and there does not need to be any recognition in the prior art that these strains are deficient in PorA or not.

Regarding arguments 2-3, whether or not Berthet’s goal was to make a composition with PorA deficient blebs and non-PorA deficient blebs, Berthet does disclose a vaccine containing strain CU-385. Vermont discloses a vaccine containing blebs from strain B:4:P1.7b,4. According to applicant's own arguments and the instant specification (see previous office actions and interview summary), Berthet discloses a multivalent bleb preparation that is a combination of CU-385 and other strains (such as H44/76). Baker suggests that a vaccine against P1.7b,4 strains would be useful. This provides a clear motivation to include the New Zealand strain in any multivalent vaccine.

Regarding argument 4, applicant has provided no evidence that the results of combining CU-385 and the New Zealand strain would be unpredictable. The letter submitted is not being

entered as applicant has failed to provide a showing of good and sufficient reasons why the evidence is necessary and was not presented earlier. See 37 CFR 1.116(e).

Regarding argument 5, the elements of the claims, as disclosed by the cited references have been described in the previous office action. Furthermore, applicant has previously acknowledged in the interview of 10/24/2007 and their response filed on 11/9/2007, and the specification states, that Berthet discloses a multivalent bleb preparation that is a combination of CU-385 and other strains (such as H44/76).

Regarding argument 6, despite applicant's arguments to the contrary, Berthet does not teach away from a multivalent vaccine containing CU-385. As stated above, applicant has claimed that Berthet discloses a multivalent bleb preparation that is a combination of CU-385 and other strains (such as H44/76).

Regarding argument 7, page 36 states that "it is also envisaged that the formulation could alternatively contain wild-type meningococcus B bleb preparations from 2 or more (preferably several) strains belonging to several subtype/serotypes (for instance chosen from P1.15, P1.7,16, P1.4, and P1.2)." The examiner fails to see how this is anything other than a disclosure of a multivalent bleb preparation.

Regarding argument 8, neither the known vaccine containing CU-385 (disclosed by Berthet and many other references) or the known vaccine containing blebs from the New Zealand strain appear to require additional meningococcal polysaccharides for serum bactericidal activity. However, this is of no consequence since the instant claims *comprise* these bleb preparations and there is no limitation that precludes additional meningococcal polysaccharides.

Regarding argument 9, as stated above, Vermont discloses a vaccine containing blebs from strain B:4:P1.7b,4. According to applicant's own arguments and the instant specification (see previous office actions and interview summary), Berthet discloses a multivalent bleb preparation that is a combination of CU-385 and other strains (such as H44/76). Baker suggests that a vaccine against P1.7b,4 strains would be useful. This provides a clear motivation to include the New Zealand strain in any multivalent vaccine.

The rejection of claims 1, 6, and 7 under 35 U.S.C. 103(a) as being unpatentable over Granoff *et al.* (PCT Publication WO 02/09643, 2/7/2002) in view of Vermont *et al.* (Infect.

Immun., 70:584-590, 2/2002) and Baker *et al.* (J. Paediatr. Child Health, 37:S13-S19, 2001), is maintained for the reasons set forth in the previous office action.

Applicant argues:

1. That one of ordinary skill in the art would not have been motivated to prepare a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA and a second bleb preparation that is not deficient in PorA.

2. That there is no motivation to combine the references because Granoff sought to elicit an immune response that was broadly reactive with diverse *Neisseria* strains and circumvent the problem of immunodominance of antigenically variable domains of PorA in PorA based vaccines. Applicant also states that Vermont examined PorA-based meningococcal OMV vaccine responses against serosubtype P1.7-2,4 in toddlers and Baker discussed efforts to obtain a P1.7b,4 PorA-specific vaccine to control New Zealand's epidemic. Applicant further asserts that one would not have been motivated to combine a vaccine which sought to circumvent the problem of immunodominant domains with a vaccine that was PorA specific.

3. That the results of the combination of references would not be predictable. Applicant has submitted a letter in response to the PCT Written Opinion that applicant asserts includes data showing the technical contribution to the art of the bleb preparations of the present invention.

4. That that cited art does not include each element as claimed. Applicant asserts that Granoff does not disclose a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA, wherein the first bleb preparation is derived from CU-385 and does not disclose a multivalent meningococcal bleb composition comprising a second bleb preparation that is not deficient in PorA, wherein the second bleb preparation is derived from strain B:4:P1.7b,4. Applicant argues that none of the strains administered by Granoff is CU-385 and none of the strains is the New Zealand strain. Applicant further argues that Granoff do not suggest that CU-385 be used in their vaccine and states that the pages cited by the examiner to support the disclosure of CU-385 merely show a summary of results from vaccine efficacy trials.

5. That Granoff points towards sequential administration of different OMVs, and in their brief reference to mixtures, they also point toward sequential administration where an initial mixture is followed by additional sequential administrations.

6. That Vermont and Baker do not make up for the deficiencies of Berthet. Applicant asserts that Vermont only evaluates the avidity maturation and IgG isotype distribution of antibodies after vaccination with a monovalent meningococcal B OMV (serosubtype P1.7-2,4) and Baker only discusses the potential value of a P1.7b,4 PorA specific vaccine in controlling New Zealand's meningococcal epidemic, but do not disclose how to make such a vaccine.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the claims are not drawn to a multivalent meningococcal bleb composition comprising a first bleb preparation deficient in PorA and a second bleb preparation that is not deficient in PorA. All that is required to meet the claim limitations is a bleb composition comprising blebs from CU-385 and blebs from strain B:4:P1.7b,4. The reasons behind combining these do not need to be the same as applicant's and there does not need to be any recognition in the prior art that these strains are deficient in PorA or not.

Regarding argument 2, applicants arguments provide no reason that one would not be motivated to combine the references. The pages in Granoff that applicant refers to discuss the fact that the immune response to *Neisseria* is strain-specific. Logically, one would include multiple strains in a vaccine to overcome this (which is one of the things Granoff suggests). Vermont discloses a bleb vaccine from the New Zealand strain and Baker provides the reason one would want to include the New Zealand strain in a multivalent preparation.

Regarding argument 4, applicant has provided no evidence that the results of combining CU-385 and the New Zealand strain would be unpredictable. The letter submitted is not being entered as applicant has failed to provide a showing of good and sufficient reasons why the evidence is necessary and was not presented earlier. See 37 CFR 1.116(e).

Regarding argument 4, it is noted that a reference is prior art for all that it teaches. The fact that Granoff does not disclose CU-385 as part of the preferred invention, does not detract from the fact that Granoff discloses vaccines containing CU-385. In fact, Granoff discloses a vaccine comprising blebs from CU-385 as an effective vaccine (a fact that is repeated in the instant specification).

Regarding argument 5, as has been stated in previous office actions, Granoff discloses mixtures. Applicant's arguments confirm this. Disclosed examples and preferred embodiments

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do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ423 (CCPA 1971).

Regarding argument 9, as stated above, Vermont discloses a vaccine containing blebs from strain B:4:P1.7b,4. According to applicant's own arguments and the instant specification (see previous office actions and interview summary), Berthet discloses a multivalent bleb preparation that is a combination of CU-385 and other strains (such as H44/76). Baker suggests that a vaccine against P1.7b,4 strains would be useful. This provides a clear motivation to include the New Zealand strain in any multivalent vaccine.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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